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Potential Triggers of Mental Distress in Cardiovascular Disease Patients

Saba Ahmed
sahmed55@binghamton.edu

Lina Begdache
State University of New York at Binghamton, lina@binghamton.edu

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Abstract

Cardiovascular disease (CVD) is a major cause of death among Americans. There are many comorbidities that exist with CVD, such as insulin-dependent diabetes, hypertension, obesity, and others. Mental distress such as anxiety and depression are comorbidities associated with CVD as well. The purpose of this study is to investigate the potential factors that could possibly affect mental health in CVD patients. A de-identified database obtained from United Health Services - Cardiology Department in Binghamton, New York included medical records of 68,647 patients. Using Chi-Square statistical analysis, many variables were associated with anxiety and depression in CVD patients. These variables included gender, age, insulin-dependent diabetes, hypertension, cancer malignant, obesity, heart failure, coronary artery disease, and long-term use of antibiotic. To our knowledge, no study has investigated the combination of these factors in association with mental distress in CVD patients. Findings from this study will have the potential to contribute to better predictive ability of mental distress in CVD patients.

Keywords: Cardiovascular disease, anxiety, depression

Introduction

Cardiovascular disease (CVD) is the number one cause of death worldwide. CVD covers a wide array of disorders, including diseases of the cardiac muscle and of the vascular system supplying the heart, brain, and other vital organs. Common cardiovascular diseases are ischemic heart disease, stroke, and congestive heart failure (Gaziano, Reddy, Paccaud, Horton, & Chaturvedi, 2006). There are many comorbidities, two or more diseases that occur together, that exist with CVD such as insulin-dependent diabetes, hypertension, obesity and others (Eckel, 1997; Tong & Stevenson, 2007). Psychological distress such as depression and anxiety are also comorbidities typically considered secondary to living with the condition (Hennekens, Hennekens, Hollar, & Casey, 2005; Joynt, Whellan, & O'Connor, 2003; Rozanski, Blumenthal, & Kaplan, 1999). Depression is typically associated with disturbances in mood, loss of interest or pleasure in previously enjoyed activities, and feelings of profound sadness and hopelessness. Anxiety is characterized by the presence of clinically significant degrees of chronic anxiety.

Some anxiety disorders include simple phobia, social phobia, generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, and acute stress disorder. Some of its manifestations are chest pain, shortness of breath, dizziness, and headaches (Ballenger, J. C., 2000).

There are multiple factors that may affect mental health in CVD patients, including comorbidities and variables such as nutrient deficiency and long-term use of antibiotics. Heart disease patients are prescribed antibiotics for several reasons, which may potentially lead to their mental distress. Many studies reveal an association of *Chlamydia pneumoniae* infection with coronary artery disease, and antichlamydial antibiotics given to cardiac patients can significantly reduce further cardiac events, such as ischemia or myocardial infarction (Gurfinkel, Bozovich, Daroca, Beck, & Mautner, 1997; Andraws, Berger, & Brown, 2005)). Antibiotics are also given to CVD patients to prevent surgical site infection in cardiac surgery or to prevent infection from cardiac electrophysiologic devices (Finkelstein et al., 2002; Chua et al., 2000). There are cases involving the risk of malnutrition in heart patients, which could lead to psychological distress. Chronic cardiac failure can contribute to a malnourished state associated with myocardial atrophy, a term known as cardiac cachexia. This can cause malabsorption, maldigestion, anorexia, and hepatic and gastrointestinal congestion. Chronic cardiac failure may also lead to diminished fat reserves and skeletal muscle (Webb, Kiess, & Chan-Yan, 1986). There can be significant morphological and functional alterations of the intestine in patients with chronic heart failure; greater intestinal permeability and an augmented bacterial biofilm may contribute to chronic inflammation and malnutrition (Sandek et al., 2007).

Cardiovascular diseases and depression are among the leading causes of the global disease burden, with CVDs accounting for 17.9 million deaths globally in 2015, and depression affecting over 300 million people worldwide. Anxiety affects many people over the world as

well, affecting approximately 272 million people. There is a high prevalence of anxiety and depression in CVD patients, with approximately 15-30% of CVD patients suffering from depressive disorders. Depression and anxiety have been found to worsen prognosis and quality of life in patients with coronary artery disease, myocardial infarction, heart failure, unstable angina, and coronary artery bypass grafting (Allabadi et al., 2019). Mental distress adds to the burden of managing CVD, therefore, it is important to study the factors that may potentially lead to mental distress in CVD patients for better treatment in the future. Previous studies have associated heart disease with psychological distress, as well as linked psychological distress to nutrient deficiency, antibiotic use, and other comorbidities such as diabetes, cancer, etc. There are even limited studies that investigated the effects of nutrient deficiencies and supplement use on mental health in CVD patients. However, to our knowledge, no study has looked into the integration of environmental factors and comorbidities that associate with mental distress in CVD patients.

Methods

A de-identified database obtained from United Health Services- Cardiology Department in Binghamton, New York included medical records of 68,647 patients. The quasi-independent variables assessed included gender, age, Body Mass Index, and comorbidities such as diabetes, hypertension, osteoarthritis, cancer, obesity, depression, anxiety and any type of CVD. Other variables analyzed were nutrient deficiencies, laboratory biomarkers (such as elevated ESR and CRP levels) and long-term use of antibiotics. Besides gender, age, and BMI, the quasi-independent variables were measured dichotomously, such as presence or absence of the condition. The other variables were categorized; gender was categorized as male or female, and age was divided into 8 categories (0-10; 11-20; 21-30; 31-40; 41-50; 51-60; 61-70; over 70). The

dependent variable was mental distress (anxiety and depression), which were both measured dichotomously. Chi-square statistical analysis was used to identify the relationship between anxiety and depression and other variables. Data analysis was performed using SPSS 25.0.

Results

There were 38,176 females and 30,467 males in the database, with the ages ranging from less than 10 years to over 70 years. From SPSS crosstab statistical analysis, gender, age, insulin-dependent diabetes, hypertension, cancer malignant, obesity, heart failure, coronary artery disease, elevated CRP, long-term use of antibiotic, and nutrient deficiency were strong predictors of depression in CVD patients.

Strong triggers of anxiety in CVD patients included gender, age, insulin-dependent diabetes, hypertension, osteoarthritis, cancer malignant, obesity, congenital disease of the heart, heart failure, cerebrovascular disease, atherosclerosis, coronary artery disease, and long-term use of antibiotic. Strong predictors are starred in the P-value column.

| | No Depression | Depression | Pearson Chi-Square Value | df | P-value |
|-----------------------------|---------------|------------|--------------------------|----|---------|
| Gender | 30467 | 38176 | 1155.194 | 3 | .000* |
| Age | 58542 | 10105 | 2924.789 | 7 | .000* |
| Insulin Dependent Diabetes | 67912 | 735 | 18.590 | 1 | .000* |
| Hypertension | 19578 | 49069 | 5045.033 | 1 | .000* |
| Osteoarthritis | 65923 | 2724 | 3.726 | 1 | .054 |
| Cancer Malignant | 68452 | 195 | 5.612 | 1 | .018* |
| Obesity | 60009 | 8638 | 46.317 | 1 | .000* |
| Congenital Disease of Heart | 68584 | 63 | 3.520 | 1 | .061 |
| Heart Failure | 66477 | 2170 | 49.637 | 1 | .000* |
| Cerebrovascular Disease | 68551 | 96 | .684 | 1 | .408 |
| Atherosclerosis | 68582 | 65 | .040 | 1 | .842 |

| | | | | | |
|-----------------------------|-------|------|---------|---|-------|
| Coronary Artery Disease | 59859 | 8788 | 464.721 | 1 | .000* |
| Elevated CRP | 68403 | 244 | 7.291 | 1 | .007* |
| Elevated ESR | 68331 | 316 | .771 | 1 | .380 |
| Long Term Use of Antibiotic | 68341 | 306 | 13.886 | 1 | .000* |
| Nutrition Deficiency | 68558 | 89 | 5.882 | 1 | .015* |

Table 1: Predictors of depression in CVD patients

*significant value (alpha=0.05); strong predictors of depression

| | No anxiety | Anxiety | Pearson Chi-Square Value | df | P-value |
|-----------------------------|------------|---------|--------------------------|----|---------|
| Gender | 30467 | 38176 | 1833.159 | 3 | .000* |
| Age | 53381 | 15266 | 9592.491 | 7 | .000* |
| Insulin Dependent Diabetes | 67912 | 735 | 65.067 | 1 | .000* |
| Hypertension | 19578 | 49069 | 12090.314 | 1 | .000* |
| Osteoarthritis | 65923 | 2724 | 56.432 | 1 | .000* |
| Cancer Malignant | 68452 | 195 | 16.235 | 1 | .000* |
| Obesity | 60009 | 8638 | 338.615 | 1 | .000* |
| Congenital Disease of Heart | 68584 | 63 | 9.206 | 1 | .002* |
| Heart Failure | 66477 | 2170 | 183.988 | 1 | .000* |
| Cerebrovascular Disease | 68551 | 96 | 4.205 | 1 | .040* |
| Atherosclerosis | 68582 | 65 | 4.949 | 1 | .026* |
| Coronary Artery Disease | 59859 | 8788 | 1174.040 | 1 | .000* |
| Elevated CRP | 68403 | 244 | 1.424 | 1 | .233 |
| Elevated ESR | 68331 | 316 | .411 | 1 | .522 |
| Long Term Use of Antibiotic | 68341 | 306 | 22.008 | 1 | .000* |
| Nutrition Deficiency | 68558 | 89 | .936 | 1 | .333 |

Table 2: Predictors of anxiety in CVD patients

*significant value (alpha=0.05); strong predictors of anxiety

Discussion

The purpose of the study was to investigate the lifestyle factors and comorbidities that may associate with anxiety and depression in CVD patients. It is conventionally known that patients living with comorbidities experience a decline in mental health; however little is known about the potential contributing factors. This study provides insight into the comorbid conditions that may potentially contribute to mental distress in CVD patients.

For instance, gender has an association with mental distress. Approximately twice as many women than men are diagnosed with major depression and generalized anxiety disorder (Leach, Christensen, Mackinnon, Windsor, & Butterworth, 2008). This is believed to be attributed to socio-demographic factors, health and lifestyle status factors, as well as psychological factors. For instance, women generally earn less than men and are less well educated, which is associated with depression. Being unemployed is correlated with a DSM-VI diagnosis of major depression. (Leach, Christensen, Mackinnon, Windsor, & Butterworth, 2008). Additionally, poorer physical health and less physical activity in women are positive mediators for the gender difference in depression and anxiety. Research indicates that men exercise more than women, and exercise is shown to reduce levels of depression (Leach, Christensen, Mackinnon, Windsor, & Butterworth, 2008). Women have greater physical morbidity than men, and poor physical health is highly comorbid with depression. Women are also more likely than men to contemplate negative experiences and thought processes, resulting in higher levels and longer episodes of depression (Leach, Christensen, Mackinnon, Windsor, & Butterworth, 2008).

In addition, there may be a connection between age and mental distress. Some evidence reveals that aging is associated with a reduction in susceptibility to anxiety and depression. Possible factors are decreased emotional responsiveness with age, greater emotional control and psychological immunization to stressful experiences (Jorm, 2000).

A link exists between diabetes and depression. In fact, clinical and subclinical expressions of depression are present in over 25% of patients with type 1 or type 2 diabetes and have adverse effects on functioning and quality of life. Studies indicate that depression is associated with poor glycemic control, particularly hyperglycemia; although it is not certain what the exact mechanism is for causing it, this is supposedly due to mind-body, or psychosomatic

interactions, in which there is reciprocal interaction between depression and hyperglycemia (Lustman et al., 2000). Anxiety is a common comorbidity of diabetes as well. Diabetes may lead to anxiety due to symptom-related worries, illness-progression concerns, fear of hypoglycemia, or even injection-phobia (Smith et al., 2012).

Likewise, hypertension associates with psychological distress. There is a 3-fold higher risk of major depression in hypertensive patients. Mechanistically, the relationship between depression/anxiety and blood pressure is thought to be due to the hyperactivity of the sympathetic nervous system. Evidence shows that plasma noradrenaline, an indirect marker of sympathetic tone, is elevated in patients with hypertension. Therefore, poor vagal control potentially increases the stress responses, which leads to mental distress in hypertensive patients (Scalco, Scalco, Azul, & Lotufo Neto, 2005).

Furthermore, there is a high prevalence of mental distress with osteoarthritis. For instance, patients with lower limb osteoarthritis suffered 2.5 times more from anxiety or depression than the general population. It has been shown that regardless of anatomical location, pain is associated with significantly high levels of anxiety and depression. However, the direction of causality is unknown; pain may contribute to psychological distress, or being distressed may cause the patient to be more aware of the pain (Axford et al., 2010).

Cancer is a factor to be considered as well. Depression occurs in 16.8% of cancer patients, but only 5.8% in the general population. Similarly, generalized anxiety disorder occurs in 9.5% of cancer patients but only in 0.9% of the general population (Tan, Beck, Li, Lim, & Krishna, 2014). The symptoms of depression and personal suffering resulting from cancer have been attributed to the disturbances in neurotransmitters and hypothalamic-pituitary-gonadal axis dysregulation. Cancer's association with mental distress are also influenced by the stress of

having the disease itself, as the patient is confronted by repeated threats to life, is receiving intense treatments, is fatigued, or is experiencing pain (Massie, 2004).

Obesity is associated with an approximately 25% increase in the odds of mood and anxiety disorders. Some proposed mechanisms suggest that the stigma attached to obesity, especially for women, could contribute to mental distress. Activity limitations due to obesity or obesity-related chronic illnesses may also increase the risk of these psychiatric disorders by reducing involvement in rewarding or pleasurable activities. Lastly, depression and obesity may be linked through some environmental cause such as child abuse, or a biological cause (Simon et al., 2006).

Cardiovascular disease may also lead to mental distress. Depressed mood is frequently experienced in cardiac patients due to them perceiving their illness as threatening one's life and well-being (Hare, Toukhsati, Johansson, & Jaarsma, 2014). Anxiety is common in CVD as well; in fact, a large proportion of depressed CVD patients suffer a comorbid anxiety disorder (Hare, Toukhsati, Johansson, & Jaarsma, 2014). There are many plausible mechanisms for triggering mental distress in CVD patients; these include alterations in the autonomic nervous system, platelet receptors and function, pro-inflammatory cytokines, endothelial function, and coagulation factors, such as fibrinogen and plasminogen activator inhibitor-1 (Hare, Toukhsati, Johansson, & Jaarsma, 2014). Depression and anxiety, however, can vary based on the type of CVD. For example, the level of depression can vary from dysthymia to grief to major depressive disorder (Hare, Toukhsati, Johansson, & Jaarsma, 2014). The prevalence of depression in patients with cardiac disease is quite variable. Mild forms of depression are found in up to two-thirds of patients in the hospital after acute myocardial infarction and major depression is generally found in about 15% of CVD patients. This prevalence is over two or three times

greater than found in the general population. It is even more prevalent in chronic heart failure patients, with it being over 20% more than the general population (Hare, Toukhsati, Johansson, & Jaarsma, 2014). However, the data analyzed in this study did not differentiate among different levels of anxiety and depression. It rather just looked into the presence or absence, making a limitation.

Furthermore, elevated levels of C-reactive protein (CRP), a marker of inflammation, is linked with psychological distress, particularly depression. Studies suggest that low-grade systemic inflammation may contribute to the development of depression. Proinflammatory cytokines activate the enzyme indoleamine-2,3-dioxygenase, which lowers production of serotonin and raises production of kynurenic and quinolinic acids (Wium-Andersen, Ørsted, Nielsen, & Nordestgaard, 2013). Decreased serotonin levels are an important factor in the pathogenesis of depression. Increased production of kynurenic and quinolinic acids leads to increased release of glutamate, which decreases production of trophic factors, including brain-derived neurotrophic factor, a factor associated with depression (Wium-Andersen, Ørsted, Nielsen, & Nordestgaard, 2013).

Although very little research had been done on mental distress and use of antibiotics, long-term use of antimicrobial drugs has been associated with mental disturbance as well. CVD patients are prescribed antibiotics for several reasons including *Chlamydia pneumoniae* infection (Gurfinkel, Bozovich, Daroca, Beck, & Mautner, 1997; Andraws, Berger, & Brown, 2005), prevention of surgical site infections (Finkelstein et al., 2002) as well as prevention of infections involving cardiac electrophysiologic devices (Chua et al., 2000). Long-term antibiotic exposure causes changes in the microbiota, leading to psychiatric side effects (Lurie, Yang, Haynes, Mamtani, & Boursi, 2015). The gut microbiota has a key role in influencing the development and

function of the nervous system through its interaction with the gut-brain axis, which integrates gut functions and links them to cognitive and emotional centers of the brain (Rogers, Keating, Young, Wong, Licinio, & Wesselingh, 2016). This connection explains high rates of comorbidity between gastrointestinal and psychiatric illnesses. For instance, mood disorders affect more than half of all patients with irritable bowel syndrome. A large population study reported that treatment with a single antibiotic course was associated with an increased risk for depression and anxiety, rising with multiple exposures (Rogers, Keating, Young, Wong, Licinio, & Wesselingh, 2016). Nonetheless, not much is known on the specifics of antibiotics triggering mental distress, so further research on this is needed.

Additionally, nutrient deficiencies add to the etiology of mental distress. There are many studies in which patients experience malnutrition due to chronic cardiac failure (Webb, Kiess, & Chan-Yan, 1986; Sandek et al., 2007) Several nutrients support mental health and brain function. These include vitamin A, vitamin C, vitamin E, vitamin D, omega-3 polyunsaturated acids, B vitamins, coenzyme Q, and minerals. Vitamins A, C, and E are antioxidants that can prevent or repair damage in the brain caused by oxidative stress, which has a role in cognitive impairment, neurodegeneration and psychiatric disorders. Vitamin D is a neurosteroid hormone that may have a role in depression due to its involvement in neuroimmunomodulation, regulation of neurotrophic factors, neuroplasticity, and brain development (Anglin, Samaan, Walter, & McDonald, 2013). Omega-3 polyunsaturated fatty acids are concentrated in the brain and are vital fatty acids for neurological development. Deficiency in omega-3 fatty acids is related to inflammation in the brain and a reduction in cerebral blood flow, which are linked to mental illness (Parletta, Milte, & Meyer, 2013). It is hypothesized that changes in brain fatty acid concentration, induced by chronic dietary omega-3 fatty acid deficiency, alters serotonergic and

dopaminergic neurotransmission (Su, Huang, Chiu, & Shen, 2003). Nonetheless, studies demonstrate omega-3 fatty acid deficiency does affect mental health; one case showed an association of lower plasma levels of omega-3 polyunsaturated fatty acids with major depression in acute coronary syndrome patients (Frasure-Smith, Lespérance, & Julien, 2004). Vitamin B6, vitamin B12, and folate are important in producing neurotransmitters and lowering high neurotoxic levels of homocysteine, so their deficiency can impair brain function and increase mental health risk. Studies have reported associations of lowered B6, B12, folate and/or elevated homocysteine in plasma with increased cognitive decline, dementia risk, and depression (Parletta et al., 2013). Coenzyme Q is an antioxidant that has anti-inflammatory properties and regular use of CoQ significantly lowers depressive symptoms in patients. The increased production of pro-inflammatory cytokines and resulting brain neuroinflammation from CoQ deficiency may therefore induce depressive symptoms (Maes et al., 2009). Additionally, low amounts of minerals such as zinc, selenium, chromium and others have also been associated with impacting mental health (Rao, Asha, Ramesh, & Rao, 2008).

Conclusion

Many variables were associated with both anxiety and depression in CVD patients. Such included gender, age, insulin dependent diabetes, hypertension, cancer malignant, obesity, heart failure, coronary artery disease, and long-term use of antibiotic. To our knowledge, this is the first study that investigates different comorbidities, nutritional factors, antibiotic use, and other variables in relation to mental health in CVD patients. Findings from this study will have the potential to contribute to better predictive ability of mental distress in CVD patients.

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